Acute Findings in an Acquired Neurosensory Syndrome

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Abstract

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Abstract
Background
In late fall 2016 diplomatic personnel residing in Havana began to present with symptoms of dizziness, ear pain, and tinnitus. As these symptoms began to appear in more personnel, an investigation revealed that these individuals reported that the symptoms often emerged after perception of very focal high frequency noise and/or a pressure wave. Methods
This is a review that examines the presenting findings of this group of patients. It examines a cohort of patients seen at the University of Miami as well as a group individual examined in Havana.
Results
All of the symptomatic individuals reported some combination of dizziness, hearing loss, difficulty staying focused/slower processing speed, tinnitus, ear pain, and/or headaches. Dizziness (92%) and cognitive complaints (56%) were the most common individual symptoms. All of the 25 affected individuals reported either dizziness or cognitive complaints, with 12/25 (48%) reporting both symptoms. All 25 individuals had at least one objective test abnormality.
Conclusion
This study focuses on the presenting symptoms of a phenomenon that has been described in one location. This is the only report which evaluates the patients during the acute phase of their symptom profile and therefore is the first report to truly characterize this syndrome. The preponderance of evidence suggests that symptoms and signs emerge after perception of a localized loud noise or pressure field. The objective findings reported for the first time here are very similar to findings in mTBI from other sources although some unique features of this exposure pattern.

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Background

Beginning in late 2016 and continuing into 2017, a number of diplomats and family members stationed in Havana, Cuba began to report complaints of sudden onset dizziness, ear pain, and tinnitus. Most of the affected individuals reported hearing an unexplained noise before the symptoms began. The affected individuals characterized the sound as being 1) loud, 2) high frequency, 3) very localized, and 4) capable of following them throughout a room. In addition, several individuals reported that if they went outside their front door, the noise immediately stopped. Others reported a sensation of pressure in certain parts of the room that could be relieved by moving a few feet away. This report is the first systematic assessment that details the acute presentation of individuals exposed in the field compared to others residing in the same location who did not report exposure. This report also outlines the acute diagnostic standards for identification of this disorder in order to facilitate recognition and proper diagnosis of an acquired injury associated with an unidentified energy source that is potentially incapacitating. This retrospective study has been approved by the IRB at the University of Miami as well as the University's HIPPA compliance office. It has also been approved by the IRB at the University of Pittsburgh.

Materials and Methods

The University of Miami conducted evaluations of all individuals who suspected they were affected by an exposure, as well as a sample of individuals who worked and lived in the same geographic area and denied any exposure. Our group examined over 140 individuals and identified 35 with a history, symptoms, and/or exposure that mirrored the injury pattern and symptoms that were reported by the early index cases. These 35 individuals reported that they had either experienced the noise and or a pressure wave or were in the same room at the same time as someone experiencing these phenomena. The remaining individuals (a larger group of over 100 individuals) denied any "exposure" to noise or experiencing a pressure sensation, either personally or as reported by those with whom they lived.

These thirty-five individuals were examined at the University of Miami, Miller School of Medicine approximately 7-60 days after the most recent exposure. There were 21 males and 14 females under the age of 64 years of age (mean: 42.3 ±11.3 years). All individuals underwent a comprehensive history and physical examination that included a standard set of history questions, a physical exam targeted to the head and neck, and a neurologic examination. Standard eye movement testing was performed as part of the neurologic exam and this testing was filmed for more precise computer analysis. Individuals were referred for other tests such as formal neuropsychological testing in accordance with the results of this history and physical. No individual was sent for testing that was not clinically indicated.

Results

The initial exam identified ten individuals (6 male and 4 female) who had no symptoms of an exposure. None of these individuals complained of symptoms and their exams were entirely normal. Only two of these asymptomatic individuals reported direct exposure; one reported a sensation of exposure to a force wave and a second heard a very brief, high-pitched noise on a single occasion. The remaining eight unaffected patients reported only indirect exposure, defined as being present in the same room at the time another individual experienced a direct exposure. This group of ten is designated as the 'unaffected group.'

The remaining 25 individuals reported direct exposure and were symptomatic (Table 1). This 'affected group' included 15 males and 10 females with the same age range and with the same average age as the lager group (Mean 43.2 ± 12.6 years of age).

The affected individuals all reported direct exposure to either noise or pressure. In many cases, their search for the origin of the noise (with the noise following them) resulted in a more prolonged exposure. A few individuals had briefer, exposures, but these occurred over several nights. The majority initially complained of ear pain (often unilateral), tinnitus, and some unsteadiness starting during or right after exposure. On presentation at our institution, the affected individuals reported a variety of symptoms that could largely be qualified as neurosensory. All of the symptomatic individuals reported some combination: 1) Dizziness/balance difficulty, 2) Hearing loss, 3) Difficulty staying focused and slower processing speed, 4) Tinnitus, 5) Ear pain, and 6) Headaches. The symptom distributions are included in Table 1. Dizziness (23/25, 92%) and cognitive complaints (14/25, 56%) were the most common individual symptoms in the affected group and all of the symptoms except headache were significantly more frequent in the symptomatic patients as compared to the asymptomatic. All of the 25 affected individuals reported either dizziness or cognitive complaints, with 12/25 (48%) reporting both symptoms. In addition, the affected group had a very high incidence of two or more symptoms. All but one of the affected individuals (96%) had two or more symptoms (that one individual only had dizziness). Sixteen individuals (64%) in the affected group had three or more symptoms. Even if headache is excluded 14 patients (56%) in the affected group presented with three or more symptoms.

The covariation between the neuro-otologic symptoms was striking. Fifteen affected individuals reported either tinnitus or hearing loss (both symptoms reported by only one person), while 14 affected individuals reported either ear pain or tinnitus (one reported both symptoms) and no one displayed all three. Because dizziness was reported by 23/25 affected individuals, it is not surprising that it is commonly associated with the other prevalent symptoms. For example, dizziness was also reported by all 8 individuals who reported tinnitus, 7/8 individuals who reported hearing loss and 5/7 individuals with ear pain. No patients in the unaffected group had more than one symptom.

Table 1: Symptoms

SYMPTOM	**Unaffected group**	**Affected Group**
Dizziness (Yes:No)	0:10 (0%)	23:2 (92%)*
Cognitive (Yes:No)	0:10 (0%)	14:11 (56%)*
Hearing Loss (Yes:No)	0:10 (0%)	8:17 (32%)*
Tinnitus (Yes:No)	0:10 (0%)	8:17 (32%)*
Ear Pain (Yes:No)	0:10 (0%)	7:18 (28%)*

Headache (Yes:No)	2:8 (25%)	6:19 (24%)
MULTIPLE SYMPTOMS		
At least 2 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	24: 1/24:1**
At least 3 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	16:9 /14:11**

*Significantly difference when compared to asymptomatic group, Fisher exact test, p<0.01
**Both values are significantly different when compared to the asymptomatic group, Fisher exact test, p<0.01

All individuals had a normal ear exam with the exception of mild erythema in the symptomatic ears of 2/7 individuals complaining of ear pain. All of the individuals with dizziness/balance disorders had abnormalities on the qualitative vestibular clinical examination either on spontaneous gaze (spontaneous nystagmus) or on rapid head thrust test (Halmagyi Head Thrust) for more than one passive head motion frequency. Postural instability was not impacted in this group of individuals nor were significant gait abnormalities identified.

Consistent with the standard of care at our facility for symptomatic patients with potential balance disorder or mild concussion, a more specific set of quantifiable tests was administered to the patients with dizziness to clarify the diagnosis (Table 2). There was a high rate of abnormality (92%) in the subjective visual vertical test (>3.2° deviation from vertical). Eleven individuals with abnormal SVV findings and suspected otolith and semicircular canal-related dysfunction were given rotational vestibulo-ocular reflex tests (horizontal semicircular canal-related function); nine of these patients also received vestibular-evoked myogenic potential testing (otolith-related functional test). The combination of SVV abnormalities and the high prevalence of deficits in both cervical and ocular Vestibular Evoked Myogenic Potential (VEMP) metrics was suggestive of an asymmetric peripheral vestibular pathology affecting the otolithic organs. The rotational chair testing demonstrated aspects of peripheral and central impairment of horizontal semicircular canal pathways, which appeared to be asymmetric.

Table 2: Clinical findings

CLINICAL FINDING (Affected Patients)	**Number Tested**	**Abnormal**	**Within Normal Limits**
Subjective Visual Vertical (SVV)	25	23	2
Chair Rotation HVOR	11	9	2
Central Vestibular Findings		6	5
Antisaccade test (abnormal error rate)	23	12	11
Cervical Vestibular Evoked Myogenic Potential) VEMP	9	7	2
Ocular VEMP	9	7	2

The anti-saccade task is an eye movement test related to executive function; it requires a subject to suppress and eye movement to a target and, instead, make an eye movement of the same magnitude in the opposite direction. The high prevalence of abnormal findings was consistent with published findings for a population with the diagnosis of acute mild concussion [1,2].

A subset of nine individuals with specific complaints was referred for a cognitive evaluation. (Table 3) Most commonly reported neurobehavioral complaints included decreased clarity of thought or “cognitive fog”, inattention, problems retrieving information on demand, especially under distracting conditions, and increased irritability and anxiety as well as overall greater difficulty regulating emotion. Formal neuropsychological testing using a comprehensive battery of tests confirmed these complaints. Decrements were observed in these individuals on measures of verbal fluency, working memory and sustained attention/vigilance, complex auditory processing requiring the ability to discriminate select stimuli from background noise, grip strength, and organizing sequential material during increasingly high levels of cognitive load. Although all individuals reported emotional distress, half formally endorsed depression and anxiety symptoms on self-report questionnaires.

Table 3 Cognitive/Neuropsychological findings

Case #	**Premorbid estimate of intellect**	**Subjective complaints**	**Neuropsychological Findings**
1	NART=114; High Average	• Forgetfulness • Mental fog/Slow performance • Difficulty with complex attention • Reduced motivation	• Diminished working memory • Slowed processing speed • Inefficient verbal learning • Reduced verbal fluency • Weak grip strength
2	NART=114; High Average	• Forgetfulness • Poor concentration/planning difficulty • Difficulty retrieving words Mood swings • Increased irritability • Lack of motivation	• Mildly impaired verbal learning and memory • Mild attentional problems • Reduced word finding • Mild depression

3	NART=117; High Average	• Slower processing • Difficulty multi-tasking • Difficulty retrieving words • Greater level of effort required to complete simple tasks	• Reduced speed of processing Weak grip strength • Diminished sustained attention/ problems sustaining mental set • Difficulty making rapid visual comparisons
4	Average	• Slower processing • Attentional problems	• Slow processing speed
5	NART=117; High Average	• Slower processing • Difficulty concentrating • Difficulty multitasking • Feeling confused • Irritability	• Reduced ability to focus in the face of competing stimuli • Episodic memory • Attention • Working memory difficulties • Weak grip strength.
6	NART=106; Average	• Forgetfulness • Slower processing • Poor concentration • Word finding difficulties • Indecisiveness • Irritability, increased tearfulness decreased interest in activities, anxiety & mood swings	• Difficulty with verbal memory • Reduced fine motor speed • Reduced ability to focus in the face of competing stimuli • Poor Grip Strength • Moderate depression • Mild Anxiety and apathy
7	NART=115; High Average	• Forgetfulness • Slower processing • Difficulty retrieving words • Mood lability & anxiety	• Decreased visual memory • Reduced verbal fluency • Weak Grip Strength
8	NART=88; Low Average	• Forgetfulness • Slower processing • Poor concentration • Difficulties with organization • Difficulty monitoring • Word finding difficulties	• Difficulty with simple verbal and visual attention, visual processing • Reduced ability to focus in the face of competing stimuli • Reduced vocabulary • Mild depression
9	Average	• Poor concentration	• Slow processing speed • Diminished abstract problem solving

Discussion

In this review, we describe the symptoms and clinical findings in a cohort of individuals who reported neurosensory symptoms after perceiving a loud, high-pitched sound and/or feeling a pressure sensation in a specific location within a room. The source of this sound/pressure sensation has not been determined but all of the affected individuals appear to be connected to the diplomatic community in Havana. The disorder appears to be fairly specific for those who actually experienced the sound/pressure sensation because no symptoms were reported by others living in the household or by a group in which no one in the household felt any of these phenomena. It is fair to say that one cannot rule out a similar presentation of symptoms in other individuals who have not reported hearing a sound or perceiving the same pressure sensation. However, we have not encountered a comparable clinical presentation in individuals who did report either sensation. Hence, the experience of sound and pressure sensations in these locations appears to be a sufficient condition for the appearance of symptoms and clinically abnormal neurosensory findings.

One must exercise considerable caution in the interpretation of a patient's causal attributions for symptoms associated with balance disorders and mTBI, including neuropsychological complaints. Attribution is obvious for overt exposure scenarios like a blast wave exposure or blunt impact to the head. However, if dizziness is due to a covert cause, the attribution is not as likely to be accurate. The dizziness, ear pain and cognitive symptoms are aversive; as in the case of conditioned taste aversion in the presence of nausea and the symptoms may be attributed to irrelevant but novel conditions that merely coincide temporally with the proximate cause. Attribution and misattribution issues for balance disorders and nausea have been reviewed elsewhere [3-6]. More recently, clinical evidence suggests that cognitive deficits in patients with otic capsule dehiscence are resolved by surgical repair [7].

The exposure responsible for these findings is unknown. It would be imprudent to exclude any potential directed or non-directed energy sources at this time. For example, perceptions of sound can occur in response to energy exposures that include microwave pulses in the audible ultrasonic range [8] or as synesthetic effects to light [9]. Pulsed microwave stimulation is known to produce ultrasonic cochlear microphonics in guinea pigs, which are suggestive of local propagation of energy in that frequency range [10]. The ultrasonic frequency range is represented at the base of the cochlea ('hook portion') in close proximity to the vestibule. Because sound activation of saccule and utricle produce cervical and ocular VEMPs [11], respectively, it is not inconceivable that resonant energy in that range could affect vestibular function. In fact, the occupational health literature indicates that intense ultrasonic radiation can produce "a syndrome involving manifestations of nausea, headache, tinnitus, pain, dizziness, and fatigue." [12] The objective findings are consistent with subacute otolithic dysfunction, raising the possibility of a vestibular concussion.

The potential mechanisms for injury by incident energy include cavitation bubble formation in body fluids. The energy released by the bubble collapse produces local jet, shock wave and acoustic emissions [13-15]. Cavitating gas bubble formation also has been associated with local tissue nitrogen accumulation in decompression illness, which may be mimicked by underwater exposure to intense sound sources[16]. Hence, internally generated, cavitation-related effects in blood and intracranial fluids (CSF, perilymph, endolymph and interstitial fluid) must be considered as possible etiologic factors after unknown energy exposures.

The pattern of findings in the symptomatic group of a vestibulopathy combined with other neurosensory findings is strikingly similar to the presentation of individuals with acute sequelae of mild traumatic brain injury following blast exposure or blunt trauma [17-20]. It does not seem imprudent to speculate that a highly specific unidentified energy exposure, perceived as a sound or pressure, could be producing an inner ear concussion or demonstrate findings suggestive of a mild traumatic brain injury (mTBI). While it is unknown how many individuals were potentially at risk, the prevalence of individuals presenting with 2 or more symptoms and the SVV abnormalities seems higher than one would expect after conventional mTBI [21]. In addition, the low incidence of headaches (around 25%) is unusual, as many studies of mTBI show that headache is one of the most common and persistent symptoms [22-24]. Perhaps the most striking clinical feature is the nearly universal evidence of otolithic impairment; such uniformity in symptoms is uncommon in mTBI cases from other sources [25,26]. Hence, the clinical presentation seems most consistent with a primary localized neurotologic injury. Furthermore, we suggest that these otolithic features be examined in symptomatic individuals to distinguish affected individuals from the “worried well.”

Conclusion

This study examines a phenomenon that, to date, has only been described in a group of diplomats in one location. The preponderance of evidence suggests that symptoms and signs emerge after perception of a loud noise or pressure field that is very localized. At the current time, the objective findings seem similar to findings in mild traumatic brain injury. However, there are a number of unique features in this group of individuals that deviate from a more traditional mTBI presentation. First, there is an extremely high incidence of objective signs of underlying otolithic abnormalities and asymmetric vestibulopathies. Second, the group is much more homogenous in presentation than most mTBI populations. Third, cognitive symptoms such as problems maintaining sustained attention, slower processing speed, difficulty multi-tasking, and word retrieval difficulties are common in mTBI. However, these cognitive problems were pervasive and consistently paired with emotional symptoms that included irritability, anxiety and depression.

Because this injury pattern could present elsewhere, it is important for individuals who care for patients to be aware of the presenting symptoms and signs. Objective, tests of otolithic and vestibular function including subjective visual vertical (SVV), vestibular evoked myogenic potentials (VEMPs), and head rotation test (head impulse tests) proved particularly helpful in this population. Based on experience with similar complaints for patients with balance disorders and acquired neurologic injuries, early identification and treatment will likely be the best method for clinical management. It is also extremely important that resources be utilized to determine the source of this pattern of signs and symptoms so that we can better understand the underlying mechanisms and better work to prevent future injuries.

Most importantly this paper provides the first and the only report of the acute presentation of this disorder, both in the clinic and in the field where the symptoms first presented. Given the unknown nature of the type and source of the energy associated with this syndrome, careful assessment and documentation of the presenting symptoms is critical. This paper describes key objective and subjective acute medical findings that distinguish affected individuals from those with other exposures and the "worried well." As with most neurosensory injuries, the diagnosis becomes confounded by a secondary cascade of events that include progression of cellular trauma, repair processes, and plasticity. In addition, the variable effects of treatment, time, and associated pathologies (such as PTSD) result in a variety of divergent symptom patterns as the syndrome progresses. As such, assessment at the acute time point after exposure provides the most accurate characterization of the injury. This precise characterization of the acute presentation provides a basis for identifying longer term progression and determining therapeutic efficacy.

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